Adaptive Continuous Template-Based Novel Manufacturing Technique for Faster Manufacturing of New APIs for Clinical Trials

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Publication date:
2012

Document Version
Publisher's PDF, also known as Version of record

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Wednesday, October 31, 2012: 1:54 PM

Allegheny III (Westin)

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The discovery of an effective and safe pharmaceutical product is based on success in clinical trials. Often, several candidate compounds targeting the same disease area are tested in order to identify the most efficacious products. This involves the manufacture of small quantities of compounds (APIs) for early delivery campaigns. Of these candidates only a few will be successful such that further development is required to scale–up the process. These API candidates are often new and complex molecules, and typically little or no information/data and (kinetic) models are available. Conventionally, for each API candidate the required data/information, model and batch process including operating conditions is developed based on an extensive experimental effort. However, this approach is time and resource intensive, especially when the number of API candidates is large, which is often the case for discovery of new pharmaceutics. Therefore, a common manufacturing platform that can be adapted for production of a series of similar API candidates with less consumption of time and resources is highly desired.

In the work reported here, a common manufacturing platform, a so-called *process template*, has been developed and used together with a systematic substrate adoption methodology (SAM) to adapt the template for a series of APIs with similar molecular functionality. The adaptation procedure includes the hazard assessment to quickly check whether the substances involved are hazardous or not, an initial solubility screen to select the right solvent, reactivity & selectivity assessment to identify the right reducing agent and catalyst, flowsheet generation to generate a process flowsheet from the template, process analysis to generate the operating conditions. The significant saving in time and resources for manufacturing of new APIs with the proposed manufacturing concept is due to several novel characteristics, for example: (i) the process template is a kind of superstructure and also consists of generic process equipments with wide operating range making it adaptable for a series of similar products; (ii) Based on a literature survey and experimentation, few candidates for the required solvent, catalyst and reducing agent which can be feasible for a series of similar products are identified beforehand which makes the sreening procedure faster; (iii) a windows of operation method has been developed for quick identification of suitable operating conditions; (iv) predictive methods and tools are employed for faster property prediction (e.g. solubility); (v) the systematic susbtrate adaption methodology provides the stepwise guidelines to the user that makes the process template adaption easier and faster. With the template based new manufacturing technique, a series of API candidates can be produced quickly for clinical trials. Therefore, on the one hand a wider range of API candidates can be tested, thus increasing the chance of identifying the right product, and on the other hand also shortening the time to market for a given compound. In addition, the template is compatible with continuous manufacturing, which is typically more efficient than batch operation.

The objective of this presentation is two-fold: First to highlight the value of the process template based new manufacturing concept and the associated methods and tools, and second to demonstrate its application using a pharmaceutical case study involving a nitro reduction.

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